REMARKS

Reconsideration of this application, as amended, is respectfully requested.

The main thrust of the current Office action is the rejection of the pending claims under 35 U.S.C. § 103(a) in which the Examiner has applied some twelve references in nine different combinations against the claims. Applicants traverse the obviousness rejections for the following reasons.

To establish a *prima facie* case of obviousness, the guidelines of M.P.E.P. § 706.02(j) and case law provide three basic criteria: (1) There must be some suggestion or motivation to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the combined references must teach or suggest all claim limitations. The guidelines of M.P.E.P. § 716.02(a) further indicate that a *prima facie* case of obviousness can be rebutted by evidence of results that are unexpected and significant, *i.e.*, the results are greater than those that would have been expected from the art to an unobvious extent and the results are of a significant, practical advantage.

In the case at hand, there is objective evidence that refutes any contention of *prima facie* obviousness. As proof of non-obviousness, the Examiner's attention is respectfully drawn to the teachings of the specification. The working examples demonstrate that the oral vaccination program of the present invention provides beneficial and unexpected results from the critical addition of the water-soluble, palatable flavorant.

The results of Example 2 are quite impressive. The data of Table 4 show that a single oral dose of $5x10^7$ of a strawberry flavored vaccine formulation (containing lyophilized *Erysipelothrix rhusiopathia*) in the drinking water gave 100% effective protection on challenge under circumstances in which the challenged control developed 100% disease. The comparative data in Tables 5 and 6 demonstrate a remarkable and unexpected difference between the flavored and unflavored vaccine formulations delivered through drinking water. Upon challenge, a single oral dose of $1x10^7$ of unflavored vaccine gave a mere 10% protection and a single oral dose of $2x10^7$ of the unflavored formulation gave a paltry 22% protection. In sharp contrast, a single oral dosage of $1x10^7$ or 2 oral doses at $1x10^7$/dose of the flavored formulation provided substantially improved protection from disease of 50% and 75%, respectively. There is no teaching in the collective art to suggest the surprisingly and significantly improved results seen

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from the oral, flavored vaccine at the lower dosages or the excellent 100% protection seen at the higher dosages from a self-administered veterinary vaccine formulation in the animals' drinking water.

Insofar as the specific rejections under 35 U.S.C. § 103(a) are concerned, the Examiner has applied the following combinations of references: (1) rejection of Claims 1-3, 5, 6, 29 and 30 as being unpatentable over Casas *et al.* in view of DE Patent 1793631 and Shimada *et al.*; (2) rejection of Claims 1-3, 5, 6, 9, 29 and 30 as being unpatentable over Clements *et al.* in view of DE Patent 1793631 and Shimada *et al.*; (3) rejection of Claims 4 and 7 as being unpatentable over Casas *et al.* or Clements *et al.* as modified by DE Patent 1793631 and Shimada *et al.*, and further in view of Grieve; (4) rejection of Claim 10 as being unpatentable over Casas *et al.* or Clements *et al.* as modified by DE Patent 1793631, Shimada *et al.*, and Grieve and further in view of Roland; (5) rejection of Claim 8 as being unpatentable over Clements *et al.* as modified by DE Patent 1793631, Shimada *et al.* and Grieve, and further in view of Frantz *et al.*; (6) rejection of Claims 1-7, 9 and 28-30 as being unpatentable over Brinton *et al.* in view of Strobel *et al.* and Collins *et al.*; (7) rejection of Claim 27 as being unpatentable over Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.*, and further in view of Mitani *et al.*; (8) rejection of Claim 10 as being unpatentable over Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.*, and further in view of Roland; and (9) rejection of Claims 1-8 and 28-30 as being unpatentable over Bricker *et al.* in view of Strobel *et al.* and Collins *et al.*

There has been a long-standing need in the veterinary field that was recognized but not yet solved to permit the efficacious, mass vaccination of animals. Under the circumstances, the large number of references is indicative of invention and the clear failure of others to solve the problem. Applicants accomplished what others failed to accomplish in prior attempts. The present method uniquely solves the long-felt problem, significantly improves the mass vaccination procedure and provides an efficacious means for protecting animals from disease.

Examining what the collective art fairly teaches to the ordinary practitioner, it will become clear that the practitioner would not have been able to arrive at the claimed invention. The art totally fails to provide suggestion or motivation of the desirability of combining the references and doing what the inventors have done. The practitioner would find real distinction between the steps of the claimed method and those elements taught in the cited references.

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In addition to the above-mentioned objective evidence of non-obviousness that rebuts the holding of *prima facie* obviousness, the combinations of references also do not teach or suggest the claimed method for the following reasons:

(1) Rejection of Claims 1-3, 5, 6, 29 and 30 as being unpatentable over Casas *et al.* in view of DE Patent 1793631 and Shimada *et al.*:

Casas *et al.* specifically relate to the use of transformed *Lactobacillus* species and, in particular, *Lactobacillus reuteri* (*L. reuteri*), as vaccine delivery vehicles. The patent provides a method for vaccination of an animal with a microorganism containing genes that are responsible for the production of proteins that provide for the aggregation of individual cells or binding to mucosa cells and can be transformed to express foreign antigens to immunize the host. The patent states that the vaccine can be ingested by an animal in a pharmaceutically acceptable carrier or it can be added to milk or milk products such as yogurt.

The oral composition taught by Shimada *et al.* contains a cationic bactericide as an active ingredient and one or both of cyclodextrin and a water-soluble flavor obtained by extracting an oil-soluble flavor with an aqueous ethanol solution. Patentees' composition is used as liquid mouth refreshers or gargles, solid mouth refreshers and the like. All of the cationic bactericides described by Shimada *et al.* are toxic substances that are not to be swallowed or consumed by the user in large quantities. The composition of Shimada *et al.* cannot be used in the veterinary field, nor is it reasonable to combine the patent's teachings with an oral vaccine that must be consumed in adequate amounts by the animal for proper immunization and protection against disease.

There is no suggestion or motivation to modify the cited references or combine their teachings and, if combined, there is no reasonable expectation of success. The fact that the oral vaccine containing the transformed *Lactobacillus* species can be added to milk or yogurt, DE Patent 1793631 describes strawberry flavorant in yogurt and milk drinks, and Shimada *et al.* adds a modified water-soluble flavor to mouth rinse does not provide any motivation to combine the teachings and prepare the oral, flavored vaccine of the present invention. Besides, there is no teaching or suggestion that the transformed *Lactobacillus* species can be eliminated from the oral vaccine taught by the primary reference or that the oral vaccine without the transformed *Lactobacillus* species would successfully immunize the animal and protect against disease.

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(2) Rejection of Claims 1-3, 5, 6, 9, 29 and 30 as being unpatentable over Clements *et al.* in view of DE Patent 1793631 and Shimada *et al.*:

Clements *et al.* are directed towards a genetically distinct mutant of *E. coli* heat-labile enterotoxin (LT) and its use as an oral, immunological adjuvant to induce mucosal and serum antibodies. For oral administration, the vaccine preparation may be reconstituted as a suspension in buffered saline, milk, or any other physiologically compatible liquid medium. Patentees state that the medium may be made more palatable by the addition of suitable coloring and flavoring agents as desired.

Clements *et al.* do not remedy the deficiencies of the teachings of Shimada *et al.* They only propose adding optional "suitable flavoring agents" to their vaccine suspension. They do not teach or suggest the advantages of this critical component of the present invention, namely, the water-soluble flavorants that make the oral vaccine of the invention more palatable to animals thereby beneficially and effectively allowing for the vaccination of more animals in a short period of time. Clements *et al.* also do not teach or imply that the oral administration of an antigen will be immunologically sufficient to protect against disease in the absence of the genetically modified bacterial toxin mLT taught as an essential ingredient of their oral vaccine.

(3) Rejection of Claims 4 and 7 as being unpatentable over Casas *et al.* or Clements *et al.* as modified by DE Patent 1793631 and Shimada *et al.*, and further in view of Grieve:

Grieve does not remedy the deficiencies of the teachings of the primary or secondary references. While the author shows that mass vaccination has been previously attempted, Grieve does not indicate that it was routine, effective or successful to administer vaccines to chickens through drinking water. In fact, the blue dye only demonstrated that approximately 80% of the flock consumed the vaccine formulation. Plus, no attempts were made to make the vaccine formulation more palatable to the birds.

Essential elements of the claimed invention require that the water-soluble, palatable flavorant is admixed with a water-soluble vehicle and the administration of the oral vaccine is by mass administration in drinking water. Clements *et al.* only teach reconstituting their vaccine preparation as a suspension. Suspensions are known to separate on standing and are typically dispensed in a small bottle or other container that needs to be shaken prior to use to disperse the solid particles and get the proper dosage. The suspension formulation of Clements *et al.* would

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not readily come to mind to be useful for the mass vaccination of animals in their drinking water. There are no solutions, as recited in the present claims, either described or implied by Clements *et al.* Plus, one would not expect the significantly improved results of the present invention in the absence of the genetically modified bacterial toxin that is taught by Clements *et al.* to be critical for adequate immunological response.

(4) Rejection of Claim 10 as being unpatentable over Casas *et al.* or Clements *et al.* as modified by DE Patent 1793631, Shimada *et al.*, and Grieve and further in view of Roland:

Roland discloses a vaccine for protecting birds against infection by avian pathogenic gram-negative microbes. The vaccine is a recombinant *Salmonella* strain expressing O-antigen of an avian pathogenic gram-negative microbe such as a pathogenic *E. coli* strain. The patent further discloses that administration of the vaccine to a bird may be by any known or standard technique, including mucosal or intramuscular injection, and preferred administration methods include oral ingestion or broncho-nasal-ocular spraying. However, the single example of using a feeding syringe highlighted by the Examiner in col. 18, lines 20-22, is by means of gastric gavage, a feeding tube in which the vaccine is forced-fed to the animal so that the animal will not be able to reject the vaccine. The experimental design described in the patent administers the vaccine first by spray and then the second booster dose is administered by oral gavage using a feeding cannula attached to a syringe, *i.e.*, the intratracheal route. That is totally different than oral administration by a syringe. Applicants teach that their syringe is useful to administer the novel flavored vaccine formulation to single animals like a horse, cat or dog in which, quite beneficially, the animal does not reject the palatable, oral vaccine. Roland had to force feed his vaccine to the animal. Otherwise, the animal would have rejected the unpleasant vaccine and spit it out. Roland did not solve the art-recognized problem of vaccine rejection by the animal.

(5) Rejection of Claim 8 as being unpatentable over Clements *et al.* as modified by DE Patent 1793631, Shimada *et al.* and Grieve, and further in view of Frantz *et al.*:

The vaccines of Frantz *et al.* contain a free, soluble *Pasteurella multocida* toxoid and/or a *P. multocida* bacterin with a cell-bound toxoid. The reference teaches that the mode of administration of the vaccines may be any suitable route that delivers the vaccine to the host but directs that the vaccine be preferably administered subcutaneously or by intramuscular injection. The reference further instructs that other modes of administration may also be employed such as

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intradermally or intravenously. The free toxoid vaccine in the examples show the formulation injected intramuscularly to swine. The patent is silent on oral administration of the vaccine. Consequently, one of ordinary skill in the art would not consider the teachings of Frantz *et al.* to be pertinent to the claimed oral method and would have no motivation to combine the parenteral vaccine formulation of Frantz *et al.* with the suspension of Clements *et al.* containing the genetically modified bacterial toxin, the flavoring in the food products of DE Patent 1793631 and the limited teachings of mass vaccination of Grieve. The practitioner simply would not arrive at the claimed invention without inventive effort.

(6) Rejection of Claims 1-7, 9 and 28-30 as being unpatentable over Brinton *et al.* in view of Strobel *et al.* and Collins *et al.*:

Brinton *et al.* describe vaccine compositions and methods for immunizing poultry in which the vaccine composition can be mass administered to the poultry through oral intake of water with or without the addition of antibiotic. The goal of the reference is to avoid the drug interactions of live vaccines with antibiotics. It is essential that the vaccine of Brinton *et al.* contain an inactivated bacterin and not live vaccines that are susceptible to antibiotics. The reference is not concerned with solving the art-recognized problem of animals' rejection of oral vaccines. Further, in Example 4, the reference notes that as the amount of water consumed increases with increasing bird age, the amount of antigen increases. Thus, the amount of immunization that the bird will receive appears to be dependent upon its age and is not shown to be a controllable factor. There is absolutely no teaching or suggestion of how to moderate or improve the amount of vaccine formulation that the bird will consume.

Strobel *et al.* teach a solid mixture or aqueous solution of amoxicillin antibacterial agent with a material that aids in its dissolution in water to render it ingestive and palatable. The water-soluble ingestible form of amoxicillin is formed by reaction with hydrocylatedpolycarboxylic acid. Strobel *et al.* indicate that to enhance the palatability of the solution, one may add flavorings *and/or* artificial sweeteners such as cyclohexyl-sulfamic acid, saccharin and aspartame. Patentees expressly teach that the artificial sweetener enhances the palatability of the hydroxyacylated amoxicillin solution. Example 6 demonstrates that the addition of sweetener increases the effective dose per unit weight of the pig.

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Collins *et al.* describe methods for diagnosis of the causative agent of Mystery Swine Disease (MSD) and antibodies to the viral agent useful in diagnosis and treatment of MSD. The patentees suggest that a MSD vaccine can be administered in a variety of dosage forms and formed into a powder or suspended in an aqueous solution such that these powders and/or solutions can be added to animal feed or to the animals' drinking water. They further suggest that the MSD vaccine powders or solutions can be suitably sweetened or flavored by various known agents to promote the uptake of the vaccine orally by the pig. However, no viable oral vaccine composition is revealed or demonstrated. The examples only show intranasally inoculated pigs, that the MSD virus was infectious and antisera were obtained. There is no illustration of a vaccine formulation that has been effectively and orally administered to the pigs to prevent the production of MSD disease let alone through mass oral administration to pigs. There are no options of sweeteners or flavoring agents described in the patent. The bare suggestion that the vaccine solution can be suitably sweetened or flavored without exemplification is not enabling prior art. It is purely an invitation to experiment further. The disclosure of the patent is not enabling to the ordinary practitioner of how to make and use the instantly claimed method. It would take undue experimentation to arrive at the claimed method.

In this combination of references, it must be examined from the point of view of what the collective art fairly teaches one of ordinary skill in the art. It is impermissible to pick and choose components from each reference without examining the context of each component in the reference and what the reference actually teaches about those components. In view of Strobel *et al.* exemplifying the importance of the sweetener in providing antibiotics to herds of animals, there is no way the ordinary practitioner would have found the same solution as Applicants when addressing himself/herself to the same problem (animal rejection of oral doses). The only reason someone would try the flavoring agent alone is with inventive curiosity, which negates obviousness. The unexpected criticality of the flavorant additive to the vaccine formulation of the present invention is neither taught nor suggested by the collective art.

(7) Rejection of Claim 27 as being unpatentable over Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.*, and further in view of Mitani *et al.*:

Mitani *et al.* specifically teach a method to obtain apple water having moderate apple flavor as a diluent for alcohol (distilled spirits) or whiskey. A person working in the veterinary

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or pharmaceutical field would not consult the reference of Mitani *et al.* to select the crucial water-soluble flavorants to be used in combination with oral vaccine formulations. Even if combined, Strobel *et al.* would teach the ordinary practitioner that, to be palatable to animals, the apple flavoring would be insufficient by itself and a sweetener must be included in the vaccine formulation. In sharp distinction, Applicants have demonstrated that the sweetener is not necessary. Quite surprisingly, the claim-recited method can be practiced with the water-soluble flavorant and provide 100% effective protection from disease in the mass vaccination program. Based on the teachings in the art, one would have no reasonable expectation of success of the claimed method in the absence of the sweetener.

(8) Rejection of Claim 10 as being unpatentable over Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.*, and further in view of Roland:

Contrary to the Examiner's hypothesis, Roland does not show that using a syringe is a routine procedure. In fact, Roland purely teaches force-feeding the vaccine to the animal by gastric gavage that utilizes the syringe device. The intratracheal route of Roland does not teach or imply the oral route. Successful immunization using a syringe to administer the flavored vaccine formulation of the present invention to the mouth of an animal without the animal spitting the dose out cannot be predicted from the forced-feeding and gastric gavage of Roland.

(9) Rejection of Claims 1-8 and 28-30 as being unpatentable over Bricker *et al.* in view of Strobel *et al.* and Collins *et al.*:

Bricker *et al.* show vaccinating turkeys via drinking water with a live *Erysipelothrix* vaccine and indicate that the vaccine provided *partial* protection against subsequent challenge with the virulent isolate of the same serotype. Collins *et al.* broadly suggest that MSD vaccine powders or solutions can be sweetened or flavored to promote the uptake of the vaccine orally by the pigs but the examples only show intranasally inoculating pigs with an infectious agent. Collins *et al.* do not demonstrate how to make or use any vaccine by successful mass vaccination of animals. There are no examples of sweetening or flavoring agents. However, since Strobel *et al.* expressly teach that the addition of sweetener increases the effective dose per unit weight of the pig, the collective art would only suggest to the ordinary practitioner that the addition of sweetener to the methods of Bricker *et al.* might improve their experimental results of partial protection against disease. There is absolutely no reason based on the combined art to add only flavoring agents to

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the turkey's drinking water of Bricker *et al.* and expect improved results, let alone achieve the significant 100% protection exemplified in the present method.

It is clear that none of the above combinations of references provide the motivation to produce the instant invention and practice the claimed method. Consequently, Applicants ask that the rejections of the pending claims under 35 U.S.C. § 103(a) be withdrawn in full.

The Examiner has also rejected Claims 1-10 and 27-30 under 35 U.S.C. § 112, first paragraph, for new matter; rejected Claims 1-10 and 27-30 under 35 U.S.C. § 112, second paragraph, for reasons set forth on pages 11 and 12 of the Office action; and objected to Claims 2, 3 and all pending claims for reasons set forth on page 16 of the Office action. Without discussion of the merits of any of these rejections and objections but to expedite matters towards allowance, the claims have been amended for the better readability thereof. It is believed that the amendment will obviate the rejections and objections of record.

The Examiner is encouraged to contact the undersigned attorney to discuss any outstanding issues that may have been inadvertently missed in this response.

Accordingly, it is believed that this application is now in condition for an allowance. Favorable treatment is respectfully urged.

Respectfully submitted,

WYETH

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